REMARKS

Claims 1, 3-7 and 16-17 have been amended in order to put them in better format. No substantive change in claim scope is intended or believed made. New claim 24 has been added, support for which is throughout the specification, especially the examples where the 17-β estradiol was the sole active ingredient used.

REJECTIONS UNDER 35 U.S.C. § 103(a)

Reconsideration and withdrawal of the rejection of claims 1, 3-4, 8, 10, 12-14, 16-18, 20 and 22-23 as being obvious from U.S. Patent No 5,866,561 to Mark T. Ungs ("Ungs") under 35 U.S.C. § 103(a) are respectfully requested.

First, all claims should be interpreted as reciting the improvement of reendothelization and vascular endothelial function, and such recitation should be given patentable weight. Improvement of reendothelization and vascular endothelial function is recited both in the preamble of claim 1, and in the recited method step (which recites the administration of the active ingredient "in an amount effective to improve reendothelization and vascular endothelial function"). The *Hirao* and *Kropa* cases cited in the pending Action do not support the position that improvement of reendothelization and vascular endothelial function is not entitled to patentable weight. In *Hirao*, the limitation in question ("process for preparing foods and drinks sweetened mildly") occurred only in the preamble, and there was no corresponding recitation in a method step. In *Kropa*, the CCPA found that the preamble term (abrasive article) was a claim limitation because it was essential to point out the defined invention. 187 F.2d at 152. The present case is even more compelling, because the term is also now part of the recited method step. With that in mind, the claims are not rendered obvious by Ungs.

The Action relies on Ungs as allegedly suggesting the application of estrogen to stenosed, dilated vessels after PTCA to prevent restenosis. Applicant respectfully disagrees, as the Examiner appears to be taking Ungs' description of the prior art out of context, while ignoring highly pertinent teachings away from the present invention in Ungs.

The reference does recognize that restenosis following PTCA can be a significant problem. However, Ungs' solution to that problem is *not* to administer a 17-β

estradiol in an amount effective to reduce restenosis to the site of dilation, or to use PTCA in the first place. Rather, Ungs teaches to avoid PTCA altogether, and instead to increase circulation by applying estrogen upstream of a stenosis *in order to promote angiogenesis*, thereby generating new blood vessels. Col. 1, line 66 to col. 2, line 9. The whole point of Ungs is to avoid the problems inherent in PTCA. Ungs thus teaches away from applicant's solution, and discourages research in the very field where applicant made his invention. That is the antithesis of obviousness. *In re Rosenberger*, 156 USPQ 24, 26 (CCPA 1967).

One of ordinary skill would not read Ungs to suggest that a 17-β estradiol alone, when applied to an injured site, can improve reendothelization and vascular endothelial function. While Ungs states at col. 1, lines 49-51 that "[a]dministration of estrogen to the stenosed, dilated region after PTCA has thus been suggested for the purposes of preventing restenosis," one would recognize that statement to be based not on any of Ungs' work, but simply a summary statement regarding the prior art disclosed in the Ungs patent. When those are considered for all they fairly teach, one would not be left with the suggestion to use a 17-β estradiol to improve reendothelization and vascular endothelial function in the presently-claimed manner. For example, Javitt (USP 5,376,652) is directed to the administration of 27-hydroxycholesterol or related compounds in liquid, solid or injectable formulations. Hughes (USP 5,516,528) is said to be directed to oral, transdermal or implant delivery of estrogen. Woods (USP 5,180,366) teaches that the prevention of restenosis requires i) promotion of the growth and division of endothelial cells, and ii) the inhibition of the growth of fibroblasts and smooth muscle cells (col. 2, lines 57-60). It further shows that estrogen is an anti-proliferation agent that may be useful in reducing the growth of smooth muscle cells (col. 5, line 20), but the Woods invention also teaches the use of a separate endothelial growth stimulator agent for promoting the growth of endothelial cells (*e.g.*, endothelial growth factor, Genentech; col. 5, line 29). Thus, one of ordinary skill would be led away from the use of only a 17-β estradiol to improve reendothelization and vascular endothelial function.

The foregoing is confirmed and amplified in the Stack Declaration of record. Dr. Stack reiterates that prevention of restenosis requires the inhibition of smooth muscle cell proliferation, as well as the promotion of vessel regeneration and repair (Paragraphs 8-9). Further, that a compound may be known as capable of reducing proliferation of smooth muscle cells would not lead one to predict that such compound would also promote reendothelialization. Indeed, Dr. Stack provides

examples of compounds that inhibit proliferation, but do *not* promote reendothelization (Paragraphs 10-14). The field is unpredictable, and the use of a 17-β estradiol as presently claimed would not have been suggested by Ungs.

Further, Ungs cannot be read as suggesting the particular dose range recited in the present claims. The Action alleges that the various claimed ranges are merely a matter of design choice. However, because the use of a 17-β estradiol as claimed is not suggested by Ungs, the particular dose ranges discovered by applicant are likewise inventive.

Finally, apparently acknowledging the differences between Ungs and the applicant's invention, the Action alleges that practice of the Ungs process would have necessarily resulted in the presently-claimed effect. Applicant respectfully disagrees. It is well established that "[o]bviousness cannot be predicated on what is unknown. . . Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). When inherency is relied on to show obviousness, the alleged inherent feature must have been obvious to those of ordinary skill when the invention was made. *Kloster Speedsteel AB v. Crucible Inc.*, 230 USPQ 81, 88 (Fed. Cir. 1986). That is certainly not the case here. As shown above, Ungs does not suggest the alleged inherent feature, and the Stack Declaration is further evidence that one would not have expected a 17-β estradiol to have the presently-claimed effect. Moreover, there is no evidence in Ungs that the presently-claimed dose of estrogen was ever actually administered, likewise undercutting any inherency argument.

Reconsideration and withdrawal of the rejection of claims 5-7, 11 and 21 as being obvious from Ungs in view of Pitha under 35 U.S.C. § 103(a) are respectfully requested. Ungs has been discussed in detail above, and for the same reasons does not make out a *prima facie* case of obviousness with respect to claims 5-7, 11 and 21. Further, Pitha does not remedy the defects in Ungs. Indeed, Pitha is relied on merely as suggesting that hydroxypropyl-beta-cyclodextrin may be used to solubilize estradiol. However, it is respectfully submitted that Pitha is not combinable with Ungs. While Pitha does discuss solubilizing estradiol in hydroxypropyl beta-cyclodextrin, that is in the context of preparing suitable topical, parenteral, oral or buccal preparations (col. 2, lines 45-61); it says nothing about the applicability of its teachings in the context of PTCA or coated stents. One of ordinary skill working with drug application via PTCA would not

look to Pitha, or be led by it or the combination of references to the inventions of claims 5-7, 11 and 21.

It is respectfully submitted that the present application is in condition for allowance.

Respectfully submitted,

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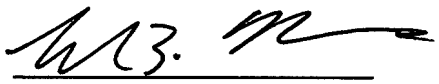
Dated: June 5, 2007 By: 

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